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Social- and Behavioral-Specific Genetic Effects on Blood Pressure Traits: The Strong Heart Family Study

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Abstract

Background—Population studies have demonstrated an important role of social, behavioral, and environmental factors in blood pressure levels. Accounting for the genetic interaction of these factors may help to identify common blood pressure susceptibility alleles.

Methods and Results—We studied the interaction of additive genetic effects and behavioral (physical activity, smoking, alcohol use) and socioeconomic (education) factors on blood pressure in approximately 3,600 American Indians participants of the Strong Heart Family Study, using variance component models. The mean and standard deviation of resting systolic and diastolic blood pressures were 123 ± 17 and 76 ± 11 mm Hg, respectively. We detected evidence for distinct genetic effects on diastolic blood pressure among ever smokers compared to never smokers (P=0.01). For alcohol intake, we observed significant genotype-by-environment interactions on diastolic (ρg=0.10, $P = 0.0003$) and on systolic blood pressures (ρg= 0.59, $P = 0.0008$) among current drinkers compared to former or never drinkers. We also detected genotype-by-physical activity interactions on diastolic blood pressure (ρg=0.35, $P = 0.0004$). Lastly, there was evidence for distinct genetic effects on diastolic blood pressure among individuals with less than high school education compared to those with 12 or more years of education (ρg= 0.41, $P = 0.02$).

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Authors Contribution: Nora Franceschini, MD, MPH had full access to all the data in the study and had final responsibility for the decision to submit for publication. NF, KMR, JWM and KN participated in the design of the study and drafted the manuscript. NF, TDD and HHHG were responsible for the statistical analysis. SAC and SL carried out the molecular genetic studies. KLS, SVS, JCU, ETL, LGB and RRF contributed with acquisition of data and revision of the manuscript. All authors read and approved the final manuscript.

Conclusions—Our findings suggest that behavioral and socioeconomic factors can modify the genetic effects on blood pressure phenotypes. Accounting for context dependent factors may help us to better understand the complexities of the gene effects on blood pressure and other complex phenotypes with high levels of genetic heterogeneity.

Keywords

epidemiology; genetics; blood pressure

The complex interplay between genes and environmental factors affecting blood pressure (BP) regulation is not well understood. Even in the era of genome wide association studies (GWAS), little progress has been made in identifying common susceptibility alleles [1,2], in part due to naive study designs that ignore the influence of social, behavioral, and environmental factors in BP regulation. Several behavioral factors can affect blood pressure in populations.[3,4] For example, smoking, physical activity and socioeconomic position (SEP) demonstrate a consistent and strong relationship with BP phenotypes including hypertension.[3] SEP may be an indirect marker of unmeasured exposures and associated behaviors (for example, stress).[5,6] SEP-specific genetic effects on BP have not been previously quantified, perhaps due to the difficulties in obtaining accurate measures of socio-economic factors. Because some of these exposures are modifiable, their interaction with genetic susceptibility to hypertension is of substantial public health importance [7] particularly among minority populations who demonstrate a high rate of hypertension and are undertreated for this condition.

Gene-environment interactions are understudied as environmental data are difficult to quantify and the estimation of interactive effects requires large sample sizes and accurate phenotypic and genotypic measures. We used data from the Strong Heart Family Study (SHFS), a large study of American Indians, which collected detailed environmental and behavioral measurements on approximately 3600 individuals within families, to study interactions among socioeconomic, behavioral, and genetic factors with health.

Methods

Population, study design and exposures

The National Heart, Lung, and Blood Institute (NHLBI) Strong Heart Family Study (SHFS) was initiated in 1998 to study the genetics of cardiovascular disease among American Indian populations.[8] The SHFS recruited family members from the original cohort of participants of the Strong Heart Study. Over 3,600 American Indians aged 14 to 93 years from 13 tribes located in Arizona, North and South Dakota, and Oklahoma were examined. The SHFS protocols were approved by the Indian Health Service Institutional Review Board, by the Institutional Review Boards of the participating Institutions, and by the Indian tribes participating in these studies.[8,9]

Participants were interviewed and examined during a clinical visit. Detailed history of exposures and SEP (education, income) were obtained using a questionnaire. Alcohol intake and cigarette smoking exposures were obtained during an interview using questions modified to fit American Indian habits and validated in a subset of the cohort. [10] Cigarette smoking was categorized as ever, current or never smoker using the following questions: During your lifetime, have you smoked 100 cigarettes or more total? Do you smoke cigarettes now?. In addition, long-term exposure was quantified using the following questions: On average, how many cigarettes do/did you usually smoke per day? When did you start smoking regularly? Alcohol intake was categorized in current vs. former or no intake using self-reported information on type, frequency and average weekly alcohol consumption. 11 Current drinkers were consuming alcohol in the 12 months prior interviews.

Physical activity was assessed using an Accusplit AE120 pedometer (Accusplit Inc, San Jose, CA) which has been shown to be a valid and reliable assessment tool for assessing step counts in a variety of laboratory and field settings. 12–19 Participants received a pedometer, instructions for wearing the pedometer, and an activity diary at their clinical examination and were asked to wear the pedometer for seven consecutive days (5 week days and 2 weekend days) and to record the number of steps taken daily in an activity diary. To ensure that participants wore the pedometer correctly, clinic staff were trained to instruct participants with large body mass index (BMI) or excess frontal body mass, which may impede the pedometer, to wear the monitor on the small of the back to aid in keeping the pedometer upright thereby reducing reporting errors. At the end of the seven-day period, participants were asked to return their pedometer and diary to the clinic in a postage paid envelope. The mean number of steps the participant took per day was calculated by averaging the number of steps recorded each day during the seven-day period. Since previous research has suggested that 3 days of activity can provide a sufficient estimate of weekly physical activity [19], participants with 3 or more days of data were included in the study. Steps per day, averaged over the week were calculated for any person who had data for 3 or more days, taking the sum of steps per day divided by the number of available days.

We used the sex-and center-specific 75% percentile of physical activity as an arbitrary cut-off point for the interaction analyses, since 7,000–8,000 steps/day correspond to approximately the average daily steps of 30 minutes of moderate-intensity activity (Table 1). [20] Individuals with incomplete 3-day pedometer measures (N=403) or less than 1,000 steps per day (N=152) were excluded from the physical activity analysis. Eliminating values this low is not uncommon since they may be considered beyond that expected in persons that are physically inactive and may likely reflect not wearing the monitor.

Blood pressure was measured using a standard protocol across the three recruiting centers. [9] Brachial seated blood pressures were measured three times by a trained technician using a mercury column sphygmomanometer (WA Baum Co) and size-adjusted cuffs. The average of the last two of the three measures was used in the analyses. Hypertension was defined using the 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as blood pressure levels of 140/90 mm Hg or higher, or the use of antihypertensive drugs. [21]

Statistical analyses

We removed outliers greater than 4.5 standard deviations from the mean for SBP and DBP. Within each center, we obtained residuals from linear regression models of SBP and DBP adjusted for age, sex, age^2 and age-by-sex interaction. We then performed an inverse normalization of the center-specific residuals and the combined residuals were used as phenotypes for the interaction analyses. We also tested models in which we adjusted for hypertension treatment, but because results were not different with or without adjustment for medications, we only reported the unadjusted models for this covariate.

For interaction analyses, we used the following categories: current smoking (yes, no), ever-smoking (yes, no), current alcohol intake (yes, no), physical activity (<75 percentile vs. ≥ 75 percentile of steps/day) and education (less than high school education vs. high school or more years of education). We did not examine the interaction effect of household income due to a large number of missing values (>50%).

We used maximum likelihood variance decomposition methods to test for genotype-by-exposure interaction by extending the univariate variance component model to include the genetic covariance of those pairs of individuals who have different exposures. [22,23] Additive genetic interactions were assessed by a likelihood-ratio tests ($\alpha = 0.05$) that compares the

likelihood of a model that includes the genotype-by-environment interaction parameter against a restricted model that excludes the interaction parameter. [23] Two restricted models were tested: a model in which the genetic correlation (ρ_g) between the pairs of individuals who have different exposures was constrained to 1.0, and a model in which the genetic variances (σ_g) among pairs of individuals who have different exposures were constrained to be equal (see also Supplemental Methods and Supplemental Table 1).

For smoking exposure, for example, the expected genetic covariance between smoking and non smoking relative pairs (*i*,*j*) is: $Cov(g_{iS}, g_{jNS}) = 2\Phi_{ij}\rho_{g(S,NS)}\sigma_{gS}\sigma_{gNS}$, where the subscripts S and NS refer to smoking and non-smoking, Φ is the coefficient of kinship between two individuals, $\rho_{g(S,NS)}$ is the additive genetic correlation between the expressions of the trait in the two groups, σ_{gS} and σ_{gNS} are the genetic standard deviations for smokers and non-smokers. If there is additive genotype-by-smoking interaction, the genetic correlation between the groups will be significantly less than 1.0 [H_A: $\rho_G(_{S,NS}) < 1.0$] and/or the genetic variances will not be equal between the groups (H_A: $\sigma_{gS} \neq \sigma_{gNS}$). When comparing models with standard deviations constrained to be equal, interpretation of significant differences are based on the assumption of an asymptotic χ_1^2 distribution for the likelihood test statistic. However, for the model with the genetic correlation restricted to one, the genetic correlation was constrained to the upper boundary of the parameter space ($\rho_g = 1.0$); thus the test statistic is as a 1/2:1/2 mixture of a χ_1^2 distribution and a point mass at zero.[23] All analyses were performed in SOLAR (San Antonio, TX).

Results

Among 3665 participants, the mean age was 40 years and 60% were female. Fifty-seven percent were ever smokers and 57% were current alcohol drinkers (Table 1). Current smokers (N=1039) had an average 9 ± 13 pack-years of smoking and former smokers (N=716) had an average exposure of 11 ± 19 pack-years. Thirty-seven percent of individuals had less than a high school education. The median level of physical activity, quantified by a pedometer over 7 days, was 5,092 steps/day among 3,110 individuals. The distribution of characteristics varied considerably across the study centers. For example, cigarette smoking and alcohol use were highest in the Dakotas and education and physical activity were lowest in Arizona (Table 1). Individuals with measured physical activity did not substantially differ from the overall cohort participants except for more often having 12 or more years of education (Supplemental Table 2). However, individuals without valid pedometer data differed substantially from those with measured data in age, co-morbidities and education (Supplemental Table 2).

Evidence for gene-by-behavioral interactions on blood pressure phenotypes

We examined the genetic architecture of the response to behaviors of BP levels using smoking, alcohol intake, and physical activity.

We detected evidence for distinct genetic effects on DBP among ever smokers compared to smokers (Table 2; *P* = 0.01). The additive genetic variance was 0.34 and 0.54 for ever smokers and never-smokers, respectively. Our inference is that the magnitude of genetic effects on DBP is distinct among smokers and non-smokers. For alcohol intake, we detected evidence for distinct genetic effects on DBP among current drinkers compared to former or never drinkers (ρg=0.10, *P* = 0.0003). Our inference is that distinct genes may influence DBP in current drinkers compared to never/former drinkers. In addition, we found evidence for distinct genetic effects for alcohol intake on SBP (ρg= 0.59, *P*= 0.0008) (Table 3). Finally, we detected evidence for distinct genetic effects on DBP among individuals in the upper quartile of physical activity compared to those in the remaining lower quartiles of physical activity (ρg= 0.35, *P* =

0.0004). These results suggest that smoking and alcohol intake behaviors as well as physical activity can modify the effects of genes influencing blood pressure traits, but in unique ways.

Evidence for gene-by-socioeconomic position interactions on blood pressure traits

We examined the genetic architecture of the response of BP levels to SEP measures using education levels as an indirect marker of unmeasured exposures and associated behaviors. In this analysis, we identified significant genotype-by-education interaction on DBP. Notably, we detected evidence for distinct genetic effects on DBP among individuals with less than high school education versus those with education equal to or higher than high school ($\rho g = 0.41$, $P = 0.02$).

Discussion

Behavioral patterns may be indirect markers of unmeasured exposures which could modify the effects of genes on phenotypes. In this study, we identified important genetic interactions of education and behavior factors on BP phenotypes. In particular, we found evidence for distinct genetic effects on DBP and SBP among individuals with different levels of smoking and alcohol exposures, physical activity and education. Smoking causes acute BP increases, but the long term effects of smoking exposure on BP measures and hypertension are inconsistent. [3] In the SHFS, current and ever smokers had higher DBP levels than nonsmokers (Supplemental Table 3) but the genotype-by-smoking interaction was significant only when comparing ever smokers to non-smokers. Former and current smokers differ on average by only 2 pack-years of exposure, so these findings may not be related to smoking exposure time but to the contribution of physiologic mechanisms or other associated behaviors in smokers (e.g. alcohol intake).[3]

Alcohol intake has been associated with increased BP independently of other lifestyle factors, such as smoking and physical activity [24–26], and the relationship may have a dose response effect. Among American Indians, current drinking was associated with a modestly increased risk of incident hypertension. [27] In our study, we observed significant genotype-by-alcohol use interactions on both DBP and SBP, suggesting exposure-specific genetic effects on BP. In addition, the magnitude of the genetic effects on DBP differed by current drinking status. These important genetic interactions with alcohol intake on BP phenotypes need to be further evaluated. Specifically, studies of the genetic interaction of quantified measures of alcohol intake on BP are needed.

Physical activity is inversely associated with hypertension. [28] Aggregated reference values, developed from a review of multiple research studies using pedometers, suggest that healthy US younger adults take between 7,000 and 13,000 steps/day while healthy older adults take between 6,000–8,500 steps per day. [20] Furthermore, it has been suggested that daily steps around 7,000 to 8,000 may be roughly equivalent to the accumulation of 30 minutes of moderate-intensity activity on a single day. [20] There is evidence that the positive influence of exercise on BP may be partly modulated by genetic influences. [29,30] In our study, we observe significant genotype-by-physical activity interaction on DBP. These findings are remarkable given the low overall level of physical activity of our cohort and the availability of only short-term measures of physical activity. We did not measure the intensity of activity, since the pedometer cannot discriminate between steps accumulated in walking, running, or stair climbing. Therefore, we were unable to determine intensity of activity and its effects on the gene-by-physical activity environment.

SEP refers to the social and economic factors influencing what position(s) a person holds within society [31], and includes measures of education, occupation, and income. [32,33] Evidence suggests that SEP effect on health may operate through poverty or limited access to material

means, increased exposure to unhealthy environments [5] and psychosocial stress related to perceptions of relative deprivation. [5,6] Studies consistently report inverse associations between SEP and BP or hypertension. [34–37] In contrast, in our study, individuals with higher education had higher DBP measures (Supplement Table 3). Using education as a proxy of SEP, we identified significant genotype-by-education interactions for DBP, suggesting that unmeasured exposures and behaviors associated with education can modify the genetic effects on BP. For example, both lower levels of physical activity and excessive alcohol use [35,36] may mediate the SEP-BP association.

This study is limited by the self-reported information on behaviors and SEP which were obtained in an interview. However, the bias of these self-reported information has been previously assessed. [10] Type I error may have occurred due to multiple hypotheses that were evaluated as part of this study. However, when applying an overly conservative Bonferoni correction of P=0.004 (P= 0.05/6 models * 2 BP traits) several significant effects were still noted, for example between alcohol intake on BP phenotypes and SEP on DBP.

In summary, our analysis suggests that behavioral factors and education attainment, a proxy for SEP, can modify the genetic effects on BP. Therefore, accounting for context dependent factors may help us to better understand the complexities of the gene effects on BP and other complex phenotypes with high levels of genetic heterogeneity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Behavioral, Socioeconomic, and Dietary Characteristics of American Indians: The Strong Heart Family Study.

Characteristics	Total (N=3665)	Dakota (N=1220)	Oklahoma (N=1210)	Arizona (N=1235)
Age, years	39.9 (17.0)	39.0 (17.1)	43.6 (17.3)	37.2 (16.0)
Female sex	2197 (60)	717 (59)	711 (59)	769 (62)
Systolic blood pressure, mm Hg	122.6 (17.1)	120.2 (16.3)	126.7 (17.3)	121.0 (17.1)
Diastolic blood pressure, mm Hg	76.2 (11.2)	75.3 (10.5)	76.8 (11.5)	76.6 (11.5)
Hypertension*	1154 (31)	286 (24)	448 (37)	420 (34)
Hypertension medications	793 (22)	217 (18)	282 (23)	294 (24)
Type 2 diabetes †	829 (23)	172 (14)	248 (21)	409 (33)
Smoking, current	1218 (33)	518 (43)	401 (33)	311 (25)
ever	2093 (57)	518 (42)	298 (25)	311 (25)
Alcohol use, current	2083 (57)	803 (66)	576 (48)	727 (60)
Physical activity, median steps per day	5092 (3255, 7463)	5607 (3716, 7926)	5089 (3255, 7695)	4485 (2842, 6636)
(25^{th}, 75^{th} percentiles) ‡	N=3110	N=1051	N=1083	N=976
Physical activity, 75^{th} percentile, N	2332	788	813	731
Education, < 12 years	1355 (37)	388 (32)	261 (22)	706 (58)
high school or equivalent or higher	2281 (63)	826 (68)	940 (78)	515 (42)

Number are means (standard deviation) or number (percentages) unless otherwise stated.

*Defined using the 7^{th} Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) classification.

†Defined as a fasting blood glucose of 126 mg/dl or higher, history of diabetes or use of diabetic medications.

‡N= individuals excluded due to records < 1,000 steps/day or incomplete 3-day measure of physical activity.

Table 2

Additive Genetic Interaction of Behavioral and Socioeconomic Factors with Diastolic Blood Pressure among American Indians: The Strong Heart Family Study.

Interaction factors	Env1	Env2 (referent)	Genetic correlation (ρ_G) ± SE (*P*-value)	Genetic standard deviation		
				Env1 (SE)	Env2 (SE)	*P*-value*
Behavioral	Smoking, ever	Never	0.63 ± 0.21 (0.05)	0.34 (0.05)	0.54 (0.06)	0.01
	Smoking, current	Past and never	0.94 ± 0.32 (0.43)	0.34 (0.09)	0.41 (0.05)	0.46
	Smoking, current†	Never	0.85 ± 0.27 (0.30)	0.38 (0.08)	0.53 (0.06)	0.11
	Alcohol intake, current	Past or never	0.10 ± 0.16 (0.0003)	0.59 (0.05)	0.38 (0.06)	0.007
	Physical activity (steps/day), lower 75th percentile	75% steps/day or more	0.35 ± 0.18 (0.0004)‡	0.47 (0.04)	0.67 (0.08)	0.04
SEP	Education, less than 12 years	12 years or more	0.41 ± 0.22 (0.02)	0.38 (0.08)	0.47 (0.05)	0.31

**P*-values for genetic standard deviation between pairs of related individuals who have different exposures.

†past smokers excluded for this analysis.

‡N= 3006 individuals. SEP, socioeconomic position; Env1 and Env2, environment 1 and 2; SE, standard error.

The 75 percentiles for physical activity are displayed in Table 1.

Table 3

Additive Genetic Interaction of Behavioral and Socioeconomic Factors with Systolic Blood Pressure among American Indians: The Strong Heart Family Study

Interaction factors	Env1	Env2 (referent)	Genetic correlation (ρ_G) ± SE (*P*-value)	Genetic standard deviation		
				Env1 (SE)	Env2 (SE)	*P*-value*
Behavioral	Smoking, ever	Never	0.83 ± 0.21 (0.11)	0.49 (0.05)	0.59 (0.06)	0.17
	Smoking, current	Past and never	1.00	0.50 (0.05)	0.52 (0.04)	0.84
	Smoking, current†	Never	1.00	0.51 (0.06)	0.62 (0.05)	0.17
	Alcohol intake, current	Past or never	0.59 ± 0.13 (0.0008)	0.57 (0.04)	0.56 (0.06)	0.92
	Physical activity, (steps/day), lower 75th percentile	75% steps/day or more	0.84 ± 0.16 (0.17) ‡	0.57 (0.04)	0.52 (0.07)	0.59
SEP	Education, less than 12 years	12 years or more	1.00	0.48 (0.05)	0.52 (0.04)	0.29

*P-values for genetic standard deviation between pairs of related individuals who have different exposures.

†past smokers excluded for this analysis.

‡N= 3006 individuals. SEP, socioeconomic position; Env1 and Env2, environment 1 and 2; SE, standard error.

The 75 percentiles for physical activity are displayed in Table 1.